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Original Article

# Patients with cystic fibrosis and normoglycemia exhibit diabetic glucose tolerance during pulmonary exacerbation☆

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**Abstract**

*Background:* Patients with cystic fibrosis and normoglycemia (CF-NGT) have higher but still "normal" glucose levels in the Oral Glucose Tolerance Test (OGTT). Respiratory exacerbation is associated with metabolic stress. The objective of this study was to assess the glucose metabolism and its relation to the steady state pulmonary function (FEV1) in patients with CF-NGT, specifically during pulmonary exacerbations (PE).
*Methods:* CF-NGT patients who were not on steroids, underwent OGTT and intravenous glucose tolerance tests (IVGTT) during PE and 4 weeks after complete recovery.
*Results:* Of the ten recruited patients two had diabetic OGTT and were excluded. The remaining normoglycemic patients displayed during PE a diabetic glucose tolerance with mean glucose levels of 233±8 and 262±11 mg/dl at 90 and 120 min respectively, compared with normal levels of 154±21and 126±20 mg/dl ($p<0.002$) during the steady state. IVGTT showed a tendency to higher first phase insulin release during PE compared with the steady state.(min 3; 305±80 vs. 216±40 pmol\l $p=0.075$). Finally, when relating the diabetic status to the general respiratory function we found a negative correlation between baseline FEV1 and glucose levels at 2 h after OGTT during PE ($r=-0.88$, $p=0.002$).
*Conclusion:* In this pilot study we show that during PE patients with CF and normal glucose tolerance exhibited early latent diabetic glucose intolerance. As this hyperglycemia presents in the later parts of the OGTT it probably results from insufficient second phase insulin secretion during PE. The negative correlation observed here between the diabetic glucose tolerance and FEV1 indicate the need of interventional studies using insulin during PE in non-diabetic patients to determine its potential benefit on the outcome from recurrent PEs.


*Keywords:* Cystic fibrosis-related diabetes; Normal glucose tolerance; Pulmonary exacerbations

## 1. Introduction

The prevalence of cystic fibrosis-related diabetes (CFRD) is steadily rising with the increased life expectancy of the patients. In a recent general survey, 19.5% of patients with cystic fibrosis (CF) had CFRD or impaired glucose tolerance and at the age of 30 years nearly 30% of patients with CF had CFRD [1–3]. Decreased pulmonary function, a decline in nutritional status, growth retardation in pubertal patients, and deterioration of the patient's general health were all shown to be associated with the presence of CFRD [4–6]. Moreover, the mortality rate among patients with CF and CFRD is six times higher compared with those without diabetes [7]. The early diabetic or impaired glucose tolerance (IGT) period may also accelerate the decline in the clinical status of patients with CF, years prior to the development of overt CFRD [4,8,9]. Therefore it has been recommended to perform an annual Oral Glucose Tolerance Test (OGTT) in patients over the age of 10 years, in order to detect early alterations in glucose homeostasis

*Abbreviations:* CF, Cystic fibrosis; NGT, Normoglycemia-normal glucose tolerance; PE, Pulmonary exacerbations; OGTT, Oral Glucose Tolerance Test; IVGTT, Intravenous glucose tolerance test; CFRD, Cystic fibrosis-related diabetes; IGT, Impaired glucose tolerance; AUC, Area under the curve.

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prior to any overt clinical manifestation and add insulin therapy accordingly [10–12].

The pathophysiology of CFRD is not fully understood, however, impaired beta-cell secretion due to pancreatic fibrosis and the progressive destruction of the pancreatic islet architecture is thought to be the main mechanism [12–14]. The role of insulin resistance in the pathogenesis of CFRD remains unclear given several conflicting studies [15–21]. In addition there is evidence for a specific role for the cystic fibrosis transmembrane conductance regulator (CFTR) protein deficiency in islet and beta-cell dysfunction [22,23].

Interestingly, even in patients with CF and normal glucose tolerance (CF-NGT) the glucose metabolism seems aberrant as the area under the glucose curve in OGTT is significantly higher and its peak plasma insulin concentration is decreased and delayed compared to healthy controls [24]. In patients with CF acute pulmonary exacerbations (PE), caused by infection and inflammation, are stressful conditions. As stress may unmask early alterations in glucose homeostasis [25,26] we have analyzed the metabolism of glucose in patients with CF who are non-diabetic with normal glucose tolerance (CF-NGT) specifically during acute PE.

## 2. Patients and methods

### 2.1. Patients

Patients with CF over 10 years of age with pancreatic insufficiency and NGT (according to the last routine OGTT performed within 3–12 months prior to the study) with no steroid therapy were included in the study. Acute PE was defined by three or more of several criteria including: an increase in cough and/or in sputum production and/or shortness of breath associated with fatigue, new findings upon chest auscultation, over10% reduction in pulmonary function and loss of appetite and weight that according to the treating physician (EK, DS) required treatment with intravenous antibiotics [27]. All the patients underwent a complete physical examination, nutritional assessment and spirometry testing before the initiation of intravenous antibiotic therapy. Intravenous glucose tolerance test (IVGTT) was done in all patients within 48 h after the initiation of the intravenous antibiotic therapy followed by OGTT on the next day. Our main outcome was to assess whether our patients fulfill the standard criteria of the definition of diabetes during exacerbation and whether they have a normal first phase insulin secretion capacity during IVGTT. These tests were repeated 4 weeks after complete resolution of the PE (usually 6 weeks following the initiation of the exacerbation). Thus, each patient served as his own control.

### 2.2. IVGTT

The test was performed using 0.5 g/kg (maximum 35 g) of 25% glucose solution, administered through a peripheral vein during 3±0.25 min [28]. Venous blood was sampled at −5, 0, 1, 3, 5, and 10 min after glucose infusion. Plasma glucose levels were recorded using a YSI 2700 glucose analyzer (Yellow Springs Instruments, Yellow Springs, OH). Insulin levels were measured by radioimmunoassay (Linco Research, St. Charles, MO).

The area under the curve (AUC) for glucose and insulin was calculated using the trapezoidal estimation. First phase insulin secretion capacity was calculated as AUC of 1+3 min of insulin in IVGTT during steady state.

### 2.3. OGTT

A standard OGTT was performed, namely, a 50% glucose solution at a dose of 1.75 g/kg body weight (maximum 75 g) was administered orally. As recurrent venous access and compliance were expected to be limited especially during steady state (as it did follow by at least 24 h the IVGTT) we chose to use the glucometer for glucose measurements in spite of its limitations (e.g. an average of 10–20% higher readings than in the laboratory). Blood glucose was sampled by an Accu-Chek glucometer (Roche Diagnostics Ltd) at baseline and at 30, 60, 90 and 120 min. The AUC was calculated using the trapezoidal estimation. The study was approved by the Institutional Review Board of the Hadassah-Hebrew University Medical Center and written informed consent was obtained from all the study participants and/or parents.

### 2.4. Statistical analysis

Results are presented as mean±SE. The non-parametrical Wilcoxon sign rank test was used for analysis and comparison of glucose and insulin levels, and for comparison of their AUC in various time points. The Spearman correlation of a number of variables was used to study the relation between the variables. Results were considered significant at $p<0.05$. All analyses were conducted using SAS 9.1.3 (SAS Institute Inc, Cary, NC).

## 3. Results

Ten patients (6 males/4 females) with CF were enrolled in the study with a mean age of 19±1.2 years [13y–23y]. All ten patients had class I and II mutations. Eight were compound heterozygotes for CF known mutations and 2 were homozygous. 7 compound heterozygotes had the combination of W1282X/DELTA F508 mutations. Pulmonary exacerbation was diagnosed based on various clinical symptoms and signs as described in the methods. Mean FEV1% was lower but not significantly different when comparing 57.2±5.7% during PE and 62.4±6.5% 6 weeks later during steady state. Mean weight (kg) was 49.68±3.1 (BMI-19.1) and ±3.2 (BMI-19.8) during PE and after treatment respectively. None of the patients received steroid therapy during the exacerbation.

### 3.1. OGTT

The results of OGTT during PE, i.e., Oral Glucose Tolerance Stress Test (OGTST) and in the steady state are shown in Fig. 1. Two of the 10 patients had diabetic OGTT in the steady state, and therefore were excluded from the study and initiated on insulin therapy. The remaining patients (excluding one who had

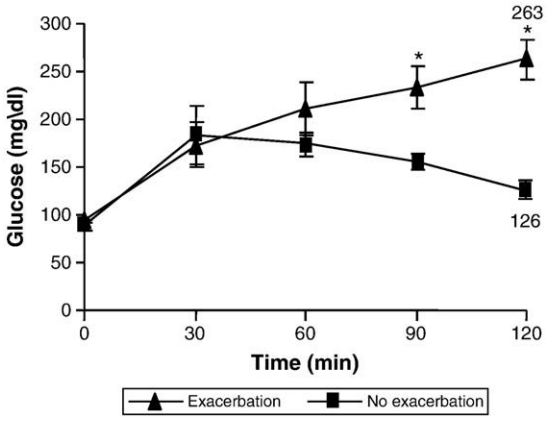


Fig. 1. Blood glucose levels in Oral Glucose Tolerance Test – OGTT during pulmonary exacerbation – (triangle) compared to OGTT during the steady state (square). *90 and 120 min $p=0.0078$.

hyperglycemia of 181 mg/dl at 120 min) displayed a diabetic glucose tolerance at the onset of PE with mean (±SE) glucose levels of 233±8 mg/dl (range 180–357) and 262±11 mg/dl (range 181–346) at 90 and 120 min respectively. After recovery from PE blood glucose levels returned to the normal range of 154±21 mg/dl, (range 119−192), 126±20 mg/dl, (range 100−141) respectively ($p=0.008$). No difference was detected between exacerbation and steady state studies in mean glucose levels at 0 and 30 min time points of OGTT. Additionally, mean AUC in OGTT during PE was higher then mean AUC during steady state (19,539±1932 vs. 14,780±1134, $p=0.008$).

### 3.2. IVGTT

Two patients did not consent to perform IVGTT due to known difficulties in their intravenous access on prior admissions. When comparing the IVGTT results during PE and following steady state we found no differences in either glucose or insulin levels. After IV glucose challenge insulin levels were not lower during PE; in fact there was a tendency (though not significant) towards higher insulin release during PE when compared with steady state. At 3 min after glucose load insulin secretion was higher (305±80 pmol/l vs. 216±40 pmol/l, $p=0.075$, Fig. 2A) and overall the ratio between the AUC of insulin and the AUC of glucose during IVGTT was higher during PE as compared with the values at steady state; (1.06±0.2 vs. 0.75±0.1 respectively ($p=0.06$)).

In order to analyze whether reduced insulin secretion capacity contributes to the high glucose levels during PE we examined the correlation between glucose levels during PE (using AUC of OGTT) and the basal insulin secretion capacity during steady state (using the early first phase [AUC of 1+3 min] insulin secretion of IVGTT). A tendency toward negative correlation was detected ($r=-0.64$, $p=0.09$) although it did not reach statistical significance (Fig. 2B).

### 3.3. Correlation between FEV1 and glucose levels during exacerbation

As CFRD has been previously associated with worsening of the general clinical status in patients with CF we analyzed the correlation between basal FEV1 (stable values that were measured during routine visits every month prior to the exacerbation) and the glucose levels during PE. A negative correlation was found between the steady state FEV1 and glucose levels during PE 2 h post OGTT ($r=-0.88$, $p=0.002$); this implied that steady state FEV1 was significantly better in those patients who displayed lower glucose levels during PE (Fig. 3).

## 4. Discussion

Patients with CF are routinely surveyed for the development of diabetes by an annual OGTT screening that detects IGT or

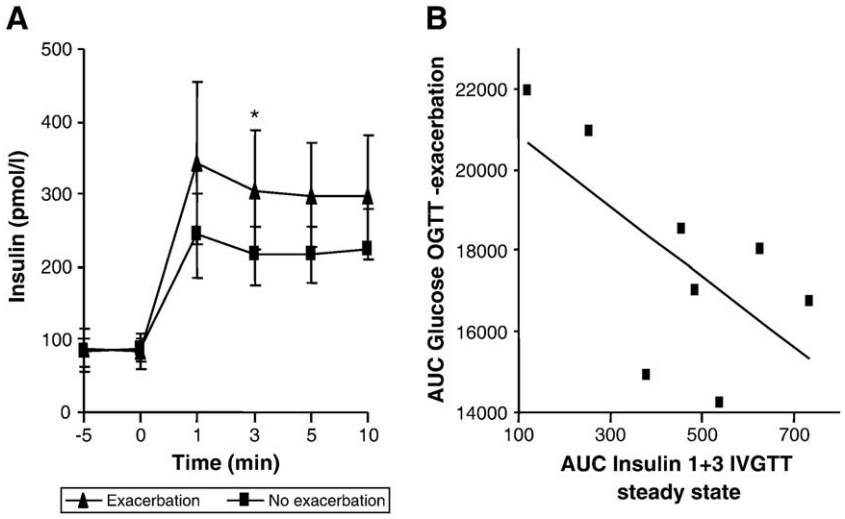


Fig. 2. A. Insulin levels during IVGTT in pulmonary exacerbations (triangle) compared to the steady state (square). *3 min time point $p=0.075$. B. Correlation between glucose levels during pulmonary exacerbations (using AUC of OGTT) and the basal insulin secretion capacity (using the early first phase [AUC of 1+3 min] insulin secretion of IVGTT) in the steady state. $R=-0.64$, $p=0.09$.

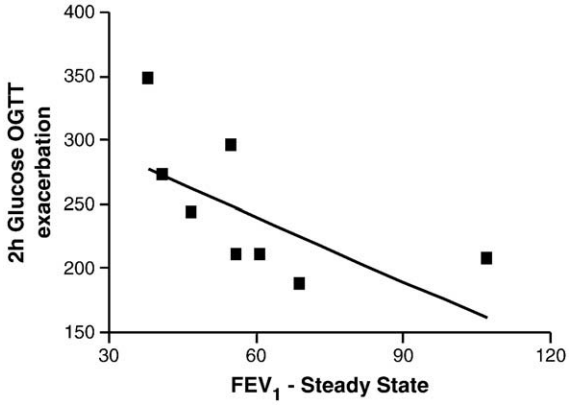


Fig. 3. Correlation between FEV1 in the steady state and the 2 h glucose levels in OGTT during pulmonary exacerbation. $R=-0.88$, $p=0.002$.

overt diabetes during pulmonary steady state [29]. Patients who carry class I and II mutations of CFTR like all of our study groups may be at higher risk for the development of CFRD [30] and probably should be more carefully monitored. To the best of our knowledge, glucose metabolism *during PE* in patients with CF but without diabetes has not yet been studied. The results of this pilot study show that patients with CF and normal glucose tolerance display a diabetic or very near glucose tolerance during PE. The studied patients who did not have glucose intolerance in the past OGTTs, exhibited hyperglycemia averaging over 230 mg/dl at 120 min of OGTT during PE which completely normalized 6 weeks later after resolution of the PE.

In order to analyze the mechanism responsible for this hyperglycemia in non-diabetic patients we evaluated the first phase of insulin secretion in IVGTT. Few studies that evaluated IVGTT in patients with CF, though not during PE, found lower levels of first phase insulin secretion compared with healthy subjects [31,32]. Tofé et al. have recently demonstrated a significant decrease in peak, first phase and total insulin secretion in patients with CF and impaired glucose tolerance (CF-IGT) compared to patients with CF and normal glucose tolerance (CF-NGT) [33]. In our patients with CF-NGT, the first phase insulin secretion during exacerbation was *not* decreased but possibly slightly increased; although no difference was observed in the IVGTT glucose levels. This finding indicated a residual beta-cell secretion capacity to meet immediate needs in conditions that are characterized by higher insulin resistance such as infection or other causes of stress [34,35]. But, although the insulin output from the beta-cells of CF-NGT patients were not decreased at the early hyperglycemic stages in both OGTT and IVGTT, it was not enough to prevent the later stage hyperglycemia observed at 90 and 120 min in the OGTT performed during exacerbation. Since insulin resistance is relatively constant along the 2 h length of OGTT, it is likely that while insulin secretion capacity in the first phase during PE was comparable to the pulmonary steady state it failed to persist for the ongoing needs at 60–120 min following the glucose load in PE. Chronic impairment of glucose tolerance and insulin secretion has been shown to correlate with the rate of decline in lung function in patients with CF [9]. Some studies demonstrated improvement in pulmonary function and nutrition status after insulin administration in patients with CF [36–39], possibly due to the anabolic effect of insulin [36,40,41]. Our observation that patients with CF with normal OGTT may have diabetic OGTT during PE may have clinical significance. These patients who are considered to be normloglycemic may experience relatively long periods of hyperglycemia during their recurrent events of infections. The exposure to hyperglycemia may adversely affect their general pulmonary and nutritional status as has been shown for CFRD.

Furthermore, in this study a negative correlation was observed between baseline FEV1 in the steady state and glucose levels at the 120 min time point in the OGTT during PE of CF-NGT patients. It could be that patients with a more severe lung disease are at the early stage of CFRD that can be detected only during stress. Alternatively the negative correlation may indicate that chronically increased glucose values during PE have an adverse impact on pulmonary function. In either way it would be important to follow these patients over a long time to see if the patients with higher glucose levels during PE are prone to develop CFRD earlier. Traditionally, OGTT during steady state has been used as the reference point for the introduction of insulin therapy. However, based on this pilot study, adding insulin during PE associated with hyperglycemia needs to be considered and may improve immediate and future outcomes. In the short term, administration of insulin may improve the glycemic state, prevent the favorable effect of hyperglycemia on the growth of respiratory pathogens [42] avoid the deleterious effect of hyperglycemia per-se during stressful conditions as in the ICU [25,26,43–46] and possibly enhance the recovery. In the long term, it may have a potential of both improving the general clinical condition of these patients and also have a protecting effect on the beta-cells by preventing the deleterious effect of chronic hyperglycemia [47,48]. The finding of only a trend rather than a significant negative correlation between glucose levels during PE and first phase insulin secretion during steady state is probably due to the relative small number of patients in our study. Recruiting patients and performing both OGTT and IVGTT in both PE and 6 weeks later in the steady state was not trivial especially given the relatively young age of the patients in our clinic and the low rates of severe exacerbations. Although this correlation did not reach statistical significance it may suggest that the patients with lower insulin secretion in steady state can maintain normal sugar during steady state however during PE not enough insulin is produced to normalize glucose levels. Further studies are needed to establish whether lower first phase insulin secretion in the steady state of CF-NGT patients can serve as a predictor for their glucose function during exacerbation.

In conclusion, our pilot study shows for the first time that during pulmonary exacerbations, patients with CF and normal glucose tolerance exhibit a diabetic glucose tolerance test. This altered glucose metabolism probably results from a limited second phase insulin secretory capacity and is associated with a more severe lung disease at baseline. Further and larger studies are needed to determine whether

insulin therapy during PE in these CF-NGT patients may have a beneficial effect on the recovery from exacerbation, the rate of decline of pulmonary function and the future development of CFRD.

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